



# Additive value of split-bolus single-phase CT scan protocol for preoperative assessment of lung cancer patients referred for video-assisted thoracic surgery

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## Abstract

We aimed to assess the additive value of the split-bolus single-phase computed tomography (CT) scan protocol to preoperatively assess patients with lung cancer, who were referred for video-assisted thoracic surgery, when compared to a standard staging CT protocol. We included 160 patients with lung cancer who underwent a split-bolus single-phase CT scan protocol (split-bolus protocol), which can acquire whole-body staging CT and pulmonary artery-vein separation CT angiography (PA–PV CTA) in a single acquisition and 160 patients who underwent whole-body staging CT (standard protocol). We compared the quality of the staging CT images of hepatic parenchyma, portal vein, and hepatic vein between both protocols. We also investigated image quality on PA–PV CTA images in the split-bolus protocol and recorded the number of patients that underwent the 3D PA–PV CTA imaging process. The split-bolus protocol for staging CT images demonstrated a slightly higher enhancement with regard to the hepatic parenchyma ( $p=0.007$ ) and hepatic vein ( $p=0.006$ ) than the standard protocol. There was no significant difference in the quality of the staging CT images between both protocols ( $p=0.067$ ). The mean CT number for the main pulmonary artery and the left atrium for the PA–PV CTA images in the split-bolus protocol were 289.1 HU and 172.8 HU, respectively. Among the images associated with the split-bolus protocol, 98.1% were of appropriate quality for 3D PA–PV CTA imaging. The split-bolus protocol is a dose-efficient protocol to acquire the staging CT and PA–PV CTA images in a single session and provides sufficient image quality for preoperative assessment in patients with lung cancer.

**Keywords** Split-bolus single-phase CT scan protocol · Lung cancer · Pulmonary artery-vein separation CT angiography · Preoperative assessment

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## 1 Introduction

Contrast-enhanced computed tomography (CT) is an indispensable method to detect abdominal–pelvic metastasis and evaluate lung cancer progression before initiating treatment [1]. Pulmonary artery–vein separation CT angiography (PA–PV CTA) to preoperatively evaluate the branches of the pulmonary artery and vein is performed before video-assisted thoracic surgery (VATS) of the lungs considering considerable inter-individual anatomical variations [2, 3]. A three-dimensional PA–PV CTA (3D PA–PV CTA) can also be used to examine the anatomy of the pulmonary artery and vein to decrease associated surgical complications and improve postoperative outcomes [4–14]. A biphasic CT scan for the pulmonary artery and vein is typically performed (at the respective optimal times during contrast enhancement) in cases that either require PA–PV separation or to obtain information on the anatomy of the peripheral branch of the pulmonary vein. [5, 6, 11]. However, one of the major concerns associated with the addition of PA–PV CTA to standard staging CT is the drastic increase in radiation. Since patients with early-stage lung cancer, who undergo VATS, are expected to demonstrate long-term survival and undergo repeated diagnostic and follow-up CT examinations, it is imperative that radiologists and radiology technicians consider reducing the radiation dose while maintaining image quality and conform to the “as low as reasonably achievable” principle.

To reduce the amount of radiation associated with the PA–PV CTA, we developed the split-bolus single-phase CT scan protocol (split-bolus protocol), in which whole-body staging CT (standard protocol) and PA–PV CTA images can be acquired in a single session. We believe that this protocol enables appropriate preoperative staging and sufficient image quality without increasing the dose of radiation.

We aimed to assess and compare the additive value of the split-bolus protocol with the standard protocol for preoperative assessment in patients with lung cancer scheduled to undergo VATS.

## 2 Materials and methods

The institutional review board approved this retrospective study. The requirement for written informed consent of patients for inclusion in this study was waived.

### 2.1 Patients

We retrospectively analyzed two cohorts. The first comprised of 160 patients who underwent the split-bolus protocol

before VATS and the second comprised of 160 patients who underwent the standard protocol to investigate the presence of metastasis. All the examinations were conducted from June 2015 to August 2018 at our hospital. Table 1 shows the patient characteristics of both protocols.

### 2.2 CT scan protocols

A 320-detector row CT (Aquilion ONE; Canon Medical Systems, Japan) was used for all the examinations. A helical CT scan was performed in the craniocaudal direction from the upper edges of the eye to the pubis. The scan parameters were as follows: tube voltage, 120 kV; X-ray tube rotation speed, 0.5 s; beam configuration, 80 × 0.5 mm; pitch factor, 0.813. The image reconstruction was performed in a 32–40 cm display field of view depending on the patient’s physique. The image noise level (standard deviation [SD]) was set at 10 Hounsfield units (HU) on the CT scanner with automatic exposure control; the tube current was changed for each patient. The images were reconstructed at a slice thickness of 7.0 mm using an iterative reconstruction algorithm (AIDR3D weak) with the standard kernel (FC14).

### 2.3 Contrast medium injection protocols

#### 2.3.1 Standard protocol

Figure 1 shows the methods used to administer the contrast media in the standard and split-bolus protocols. Iodine was used as the contrast medium (Omnipaque, 300 mg/mL; Daiichi-Sankyo, Tokyo, Japan) and was administered at 500 mg/kg body weight using an automatic power injector (Dual Shot GX 7; Nemoto Kyorindo Co. Ltd., Tokyo, Japan). In the standard protocol, the total volume was administered over 90 s, following which a CT scan was performed after a gap of 90 s (Fig. 1a).

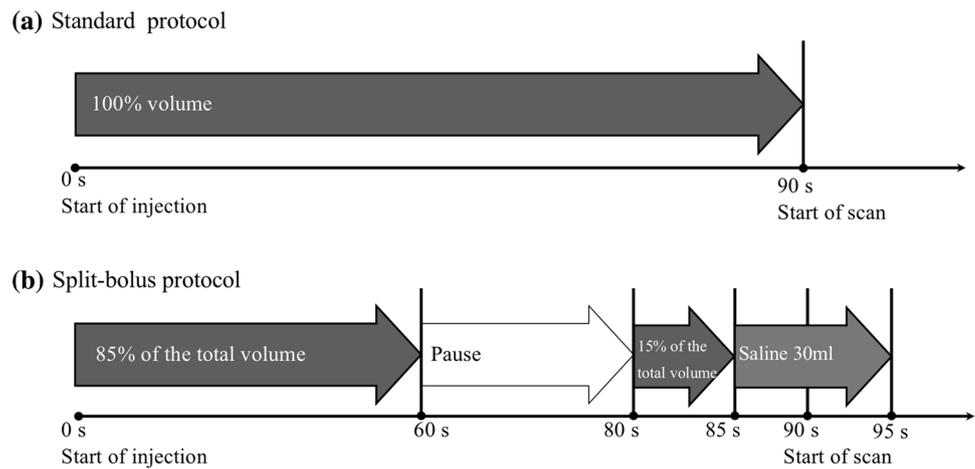
#### 2.3.2 Split-bolus protocol

In the split-bolus protocol, the first step was to enhance the view of the pulmonary artery/vein and abdominal–pelvic

**Table 1** Patient characteristics in the standard and split-bolus protocol groups

	Standard protocol	Split-bolus protocol	<i>p</i> value
Patient number	160	160	0.359
(Male:female)	(94:66)	(102:58)	
Age (years)	68.4 ± 10.1	67.8 ± 10.3	0.545
Mean ± SD (range)	(30–89)	(24–89)	
Body weight (kg)	57.0 ± 10.2	57.7 ± 10.3	0.549
Mean ± SD (range)	(32–94)	(31–91)	

**Fig. 1** Contrast medium injection method in the standards protocol (a) and split-bolus protocol (b). CT scan was started after the injection at 90 s



region with administration of 85% of the total volume for 60 s followed by an interval for 20 s; in the second step, only the pulmonary artery was additionally re-enhanced by administering the remaining 15% for 5 s (after 80 s from the first step) followed by administering 30 mL of saline over 10 s (total 95 s). The difference in the CT enhancement between the pulmonary artery and vein was due to the sequential split-bolus administration. In the third step, a CT scan was performed 90 s after starting contrast medium injection when the contrast medium had reached the pulmonary artery (Fig. 1b).

#### 2.4 3D PA–PV CTA (volume rendering) creation

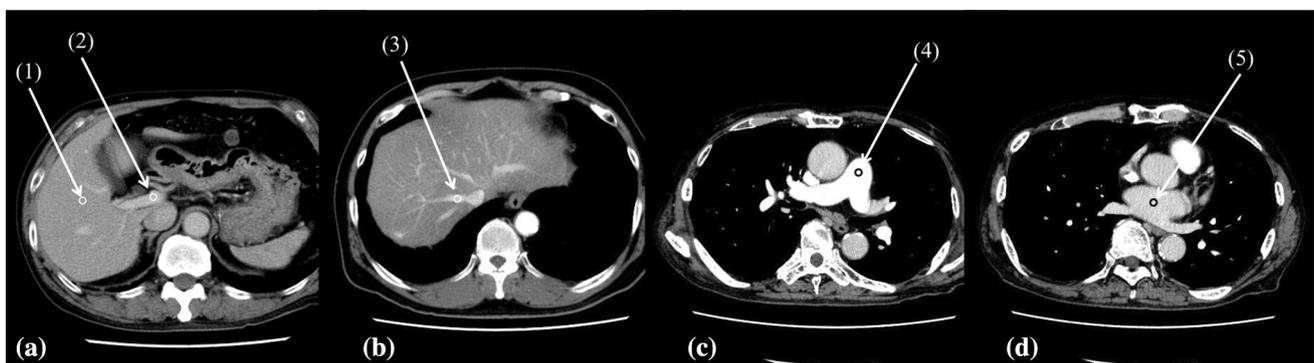
Three-dimensional PA–PV CTA imaging, using the split-bolus protocol, was performed by reconstructing the CT images from the apex to the bottom of the lung with a slice thickness of 0.5 mm and slice interval of 0.4 mm. The volume data set was then transferred to a workstation (ZIO-STATION2, AMIN Corporation, Tokyo, Japan). The rendered 3D volume was created from commonly used basic

functions such as object selection and manipulation of the opacity and transparency. Each color-coded segment for pulmonary artery (red), pulmonary vein (blue), bronchus (yellow), and tumor (green) was created on the workstation. Volume rendering fusion images were created for all segmented anatomic structures (pulmonary artery, pulmonary vein, bronchus, and tumor) and displayed to improve the visualization of complex anatomical and three-dimensional relationships.

#### 2.5 Image analysis

##### 2.5.1 Staging CT images

We measured the CT numbers in the staging CT images for quantitative image analysis by placing a 3.0 mm diameter region-of-interest (ROI) in the hepatic parenchyma, portal vein (Fig. 2a), and hepatic vein (Fig. 2b) in the standard and the split-bolus protocols ( $n = 320$ ) using ImageJ 1.45 (National Institutes of Health) [15].



**Fig. 2** Measurement regions of CT numbers. a ROI positions for hepatic parenchyma (1), portal vein (2). b ROI positions for hepatic vein (3). c ROI positions for main pulmonary artery (4). d ROI positions for left atrium (5)

Alternatively, qualitative image analysis was performed by evaluating the visual equivalence of the staging CT images between the split-bolus protocol and the standard protocol with a CT console display (Canon Medical Systems, Japan). Images of 100 patients (50 patients each from the split-bolus and standard protocols) were randomly assigned for visual evaluation (Table 2). Five radiologists experienced in CT examination (years of experience: 8, 11, 12, 22, and 29, respectively) rated the overall image quality using a 5-point scale (5, excellent; 4, very good; 3, adequate; 2, suboptimal; 1, inadequate). The overall image quality was defined as the contrast effect of the hepatic parenchyma, aorta, portal vein, and the hepatic vein.

### 2.5.2 PA–PV CTA images

The images were quantitatively analyzed by, the CT numbers of the pulmonary artery (Fig. 2c) and left atrium (Fig. 2d) were measured in the 160 patients from the split-bolus protocol group. To evaluate the central (main pulmonary artery and the left atrium) and peripheral vessels (lower lobe pulmonary artery, lung apex vein, and basal vein of lower lobe),

**Table 2** Patient characteristics that were included in the visual evaluation

	Standard protocol	Split-bolus protocol	<i>p</i> value
Patient number	50	50	0.836
(Male:female)	(31:19)	(32:18)	
Age (years)	68.4 ± 13.5	67.0 ± 12.6	0.603
Mean ± SD (range)	(24–86)	(30–87)	
Body weight (kg)	55.3 ± 11.2	57.5 ± 12.1	0.338
Mean ± SD (range)	(34–90)	(32–94)	

the CT numbers were measured by setting an ROI of 2.0 mm diameter.

Qualitative image analysis was performed, the ease of 3D PA–PV CTA image creation was recorded by 1 reader using a 4-point scale (4, easy; 3, neutral; 2, difficult; and 1, impossible). In addition, the creation time of the 3D PA–PV CTA image was measured.

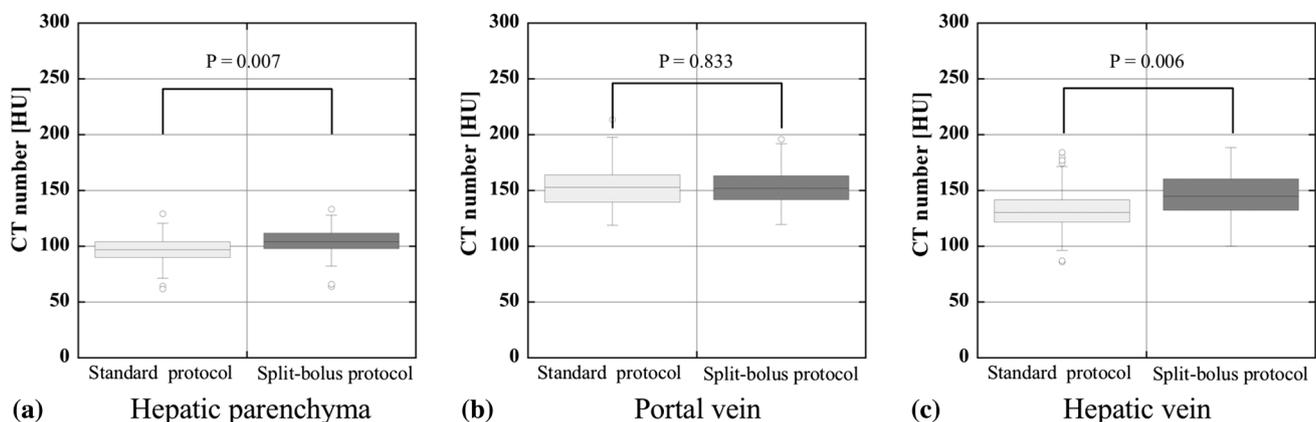
### 2.6 Statistical analysis

The patient's age and body weight, qualitative image analysis of staging CT and PA–PV CTA images were tested for normality and equality of variances using the Levene's and Shapiro–Wilk tests. A Chi squared test was used to compare the proportion of men and women in the standard and split-bolus protocol groups. A 2-tailed student *t* test was used to compare the age and body weight of patients and a paired *t* test was used to compare contrast enhancement of the main pulmonary artery vs. left atrium and the peripheral pulmonary artery vs. peripheral pulmonary vein. An unpaired *t* test was used to perform a quantitative image analysis of the staging CT images. The Mann–Whitney *U* test was used to perform a qualitative image analysis of the staging CT images. A commercially available software (SPSS® Statistic v. 25.0; IBM Corp. New York) was used to perform all the statistical analyses; *p* < 0.05 was considered indicative of a statistically significant difference.

## 3 Results

### 3.1 Staging CT images

Regarding quantitative image analysis, Fig. 3 shows the CT numbers of the hepatic parenchyma (Fig. 3a), the portal

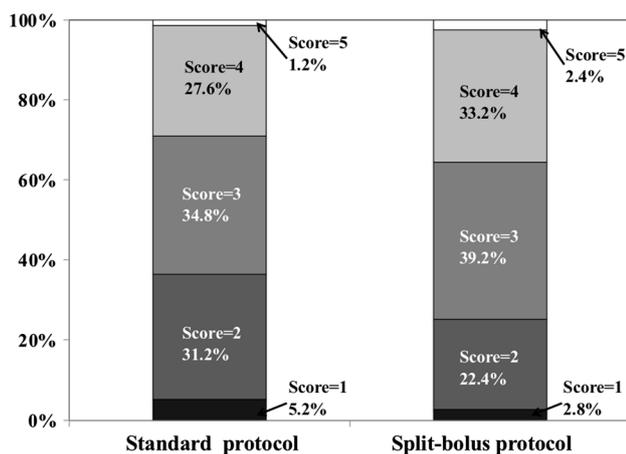


**Fig. 3** CT number measurements of hepatic parenchyma (a), portal vein (b), and hepatic vein (c). CT numbers of hepatic parenchyma, portal vein, and hepatic vein or standard protocol were 96.4 ± 10.9

HU, 153.3 ± 17.5 HU, 132.1 ± 18.4 HU; and those for split-bolus protocol were 104.5 ± 10.6 HU, 152.6 ± 14.9 HU, 145.3 ± 18.5 HU

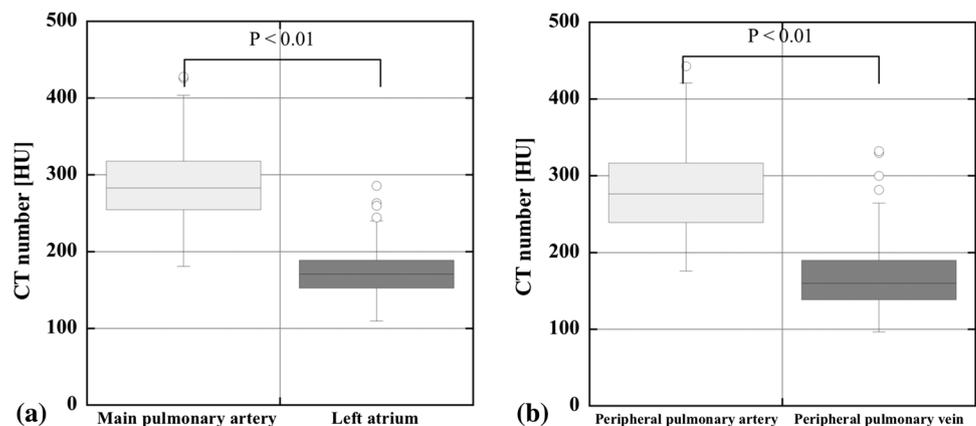
vein (Fig. 3b), and the hepatic vein (Fig. 3c) in the standard and split-bolus protocol groups. Compared with the standard protocol, the split-bolus protocol demonstrated slightly higher numbers for hepatic parenchyma ( $p=0.007$ ; difference between 2 mean numbers, 12.63 HU; 95% confidence interval for the difference between 2 means, 3.43–21.84 HU.) and the hepatic vein ( $p=0.006$ ; difference between 2 mean numbers, 20.27 HU; 95% confidence interval for the difference between 2 means, 5.83–34.71 HU). In the case of the portal vein, there was no significant difference between the 2 protocols regarding the CT number ( $p=0.833$ ; difference between 2 mean numbers,  $-0.66$  HU; 95% confidence interval for the difference between 2 means,  $-4.12$  to 2.81 HU).

Considering qualitative image analysis, Fig. 4 shows the visual evaluation scores of the staging CT images in the standard and split-bolus protocol groups. The average ( $\pm$ SD) scores for both protocols were  $2.9 \pm 0.53$  and  $3.1 \pm 0.54$ , respectively; the between-group difference was not statistically significant ( $p=0.067$ ). However, 33.2%



**Fig. 4** Visual evaluation scores (VAS) of staging CT images in the standard and split-bolus protocol groups

**Fig. 5** CT number in the main pulmonary artery and the left atrium (a) and CT number in the peripheral pulmonary artery and vein (b). Peripheral pulmonary artery is a lower lobe pulmonary artery with a diameter of 3–5 mm. Peripheral pulmonary vein is an apical segmental vein or basal segmental vein with a diameter of 3–5 mm



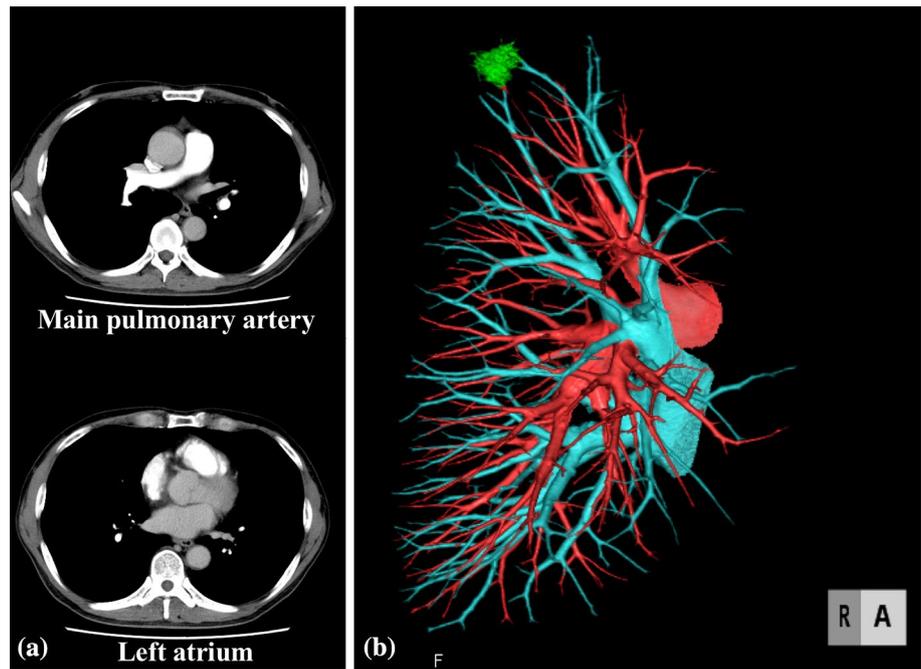
and 2.4% of the images in the split-bolus protocol had a score of 4 and 5, respectively; these were slightly higher than the corresponding percentages in the standard protocol group.

### 3.2 PA–PV CTA images

With regard to quantitative image analysis, Fig. 5a shows the CT numbers of the main pulmonary artery and the left atrium in the split-bolus protocol. The mean ( $\pm$ SD) numbers of the main pulmonary artery and left atrium were  $289.1 \pm 50$  HU and  $172.8 \pm 30.5$  HU, respectively. The number of patients and the differences in their corresponding CT numbers between the main pulmonary artery and the left atrium were as follows: 132 patients at over 100 HU, 25 patients at 80–100 HU, and 3 patients less than 80 HU, and the mean difference of CT number was 116.3 HU. There was significant difference in the CT number of the main pulmonary artery and the left atrium ( $p < 0.01$ ). Figure 5b shows the CT numbers of the peripheral pulmonary artery and the peripheral pulmonary vein. The mean ( $\pm$ SD) numbers in both images were  $279.8 \pm 54.6$  HU and  $169.1 \pm 44.1$  HU, respectively. The difference in the CT numbers between the peripheral pulmonary artery and the peripheral pulmonary vein was 110.7 HU, and a high-contrast difference was noted between the peripheral pulmonary artery and vein. Figure 6 shows an example of the CT images for the main pulmonary artery, the left atrium (Fig. 6a), and the 3D PA–PV CTA images (Fig. 6b). In the 3D PA–PV CTA image, the anatomical separation of the PA–PV and the location of the tumor were clearly observed using the split-bolus protocol.

Considering qualitative image analysis, the ease of creating a 3D PA–PV CTA image was 81.3% (130/160), 16.9% (27/160), 1.9% (3/160), and (0/160) 0% for scores of 4, 3, 2, and 1, respectively. The mean creation time of 3D PA–PV CTA image was 10 min 20 s for score 4, 14 min 54 s for score 3, and 32 min 58 s for score 2.

**Fig. 6** CT images (a), and 3D volume-rendered image (c)



## 4 Discussion

The split-bolus protocol was analyzed on the basis of two parameters: (1) quality of images compared to the standard protocol for lung cancer staging and (2) image quality of the PA–PV CTA images. In the split-bolus protocol with the single-phase method, the contrast medium was administered in multiple steps and a single whole-body staging CT was performed. Therefore, the PA–PV CTA image, without temporal and spatial deviations induced by breathing and heart-beats, and the staging CT images could be obtained simultaneously.

The CT numbers of the main pulmonary artery and the left atrium were  $289.1 \pm 50$  HU and  $172.8 \pm 30.5$  HU, respectively. The CT numbers of peripheral pulmonary artery and vein were  $279.8 \pm 54.6$  HU and  $169.1 \pm 44.1$  HU, respectively. The difference in the CT numbers between the pulmonary artery and vein with the split-bolus protocol was 116.3 HU at the main portion and 110.7 HU at the peripheral portion. Previous studies have reported CT numbers of the pulmonary artery for evaluation of pulmonary embolus to be approximately 245–317.9 HU [16–19]. Although these reports were not specifically associated with 3D imaging, these values serve as the indices for optimal contrast enhancement for the pulmonary artery. In our study, the pulmonary vein had a slightly lower CT number. However, it is our understanding that the contrast between the blood vessel and the vicinity is more important while generating a 3D image of a blood vessel.

The CT numbers for hepatic parenchyma with the split-bolus protocol and standard were  $104.5 \pm 10.6$  HU

and  $96.4 \pm 10.9$  HU, respectively. The CT enhancement of the staging CT images with the split-bolus protocol was almost equivalent or slightly higher than that with the standard protocol; a similar tendency was observed on visual evaluation. Several studies have reported the CT number of hepatic parenchyma for detection of metastasis. In a meticulous examination of patients with confirmed malignant tumors, Borgen et al. [20] administered 100 mL of 300 mg iodine/mL contrast medium over a period of 30 s (mean BMI 27.7 kg/m<sup>2</sup>) and performed a scan for 94–98 s; the mean CT number of hepatic parenchyma was  $97.7 \pm 19.3$  HU. Furthermore, for the diagnosis of metastatic liver tumor, Nakaura et al. reported that the CT number of hepatic parenchyma was  $114 \pm 13$  HU; a scan was performed at 70 s after administering the contrast medium (mean dose: 555 mg iodine/kg) over 50 s [21]. These reported data were relatively similar to our quantitative results obtained with the split-bolus protocol. Therefore, we believe that the contrast enhancement for the hepatic parenchyma was sufficient and that the split-bolus protocol is appropriate for the detection of abdominal–pelvic metastasis.

In our study, we employed 120-kV images in consideration of the staging CT image quality. Increasing the differences in the CT numbers between the pulmonary artery/vein, dual-energy CT, and low-tube-voltage techniques may be considered as an additional feasible approach [22–25]. Currently, our CT scanner does not allow for dual-energy mode in the staging CT due to dual spin (two rotations) technology. We may need to confirm the optimal staging CT image quality with low-tube-voltage techniques in the next step.

There were several limitations in our study. First, the split-bolus protocol did not include methods to correct the circulatory dynamics of the patients, such as a bolus tracking system and test bolus technique due to the long administration time. Second, even though we used a bolus 30 mL of saline, the contrast medium was retained in the superior vena cava in some patients [26, 27]. Further improvement for more effective utilization may be required in the next study. Third, regarding reader selection for qualitative image analysis, we assigned only one reader, and not multiple readers, considering variability across readers. Finally, the number of patients was relatively small. Further large-scale studies are required to validate our results.

In conclusion, the split-bolus protocol is a dose-efficient protocol which enables the staging CT and PA–PV CTA in a single session and provides sufficient image quality for preoperative assessment of patients with lung cancer.

### Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all study participants.

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